CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 20-789

MEDICAL REVIEW(S)

- Review
and Evaluation of Clinical Data

NDA:	20-789
Sponsor:	Athena
Drug:	Zonisamide 100 mg capsule
Proposed Indication:	Adjunctive therapy in the treatment of partial seizures with and w/o secondary generalization.
Material Submitted:	Original NDA
Serial No.:	001
Correspondence Date:	March 27, 1997
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APPEARS THIS WAY
ON ORIGINAL

1. Introduction:

Zonisamide is a sulfonamide which is chemically unrelated to other antiepileptic drugs (AEDs). There reportedly is minimal carbonic anhydrase inhibiting activity associated with Zonisamide. Zonisamide has been developed as adjunctive therapy for the management of partial seizures with and without secondary generalization in adult patients with epilepsy.

2. Background:

Zonisamide was originally synthesized and initially developed by [redacted] The initial U.S. IND [redacted] with the Food and Drug Administration (FDA) was filed in March 1982 by [redacted] Initial studies conducted by [redacted] suggested that zonisamide was effective in treating patients with refractory epilepsy. In 1987 [redacted] discontinued the drug's development in the U.S. following the appearance of a number of renal calculi cases in the clinical trial data (13 out of 505 patients). Development was continued in Japan, and Zonisamide was approved in Japan in 1989. During this development 2 cases of renal stones were reported in 1,008 subjects. In post-marketing studies over a 3 year period only one case of renal stones was confirmed in 2,444 patients.

3. Materials Reviewed:

The documents provided by the sponsor for review were of three types. The first consisted of the NDA, specifically the clinical sections, volumes 1, 38, 40, 52- 305, 313, and 324. In addition, portions of the NDA were provided to the reviewer in electronic format (WordPerfect ® documents). These sections included: Application Summary, Summary Of Non-clinical Pharmacology And Toxicology Data, Summary Of Clinical Pharmacology, Summary Of Human Pharmacokinetics,., Integrated Summary Of Safety, , Integrated Summary Of Effectiveness, Placebo- Controlled Clinical Trials (Dainu-922, 720-02266 (9 12-US), And 720-02275 (912-Eur), Case Report Tabulations, and Proposed Text Of The Labeling (Not Annotated / Annotated). The third source of information was in the form of SAS data sets which included: Seizure Data Set for Warner Lambert Double Blind Study (912-US) (SEIZUSDB), Seizure Data Set for Warner Lambert European Double Blind Study (912-EUR) (SEIZEUR), Seizure Data Set for iBRD Double Blind Study (922-US) (SEIZ922), Seizure rates data sets (A1, A2, B1, B2, C1, and C2), AED Dosing (DOSING), Patient Demographics/Termination (PATIENT), and AED Plasma Levels (PLASMA). Additional data sets were provided for Adverse Events, Serum Chemistry Clinical Laboratories, Hematology Clinical Laboratories, Urinalysis Clinical Laboratories, and Vital Signs, but were not reviewed for evaluation of clinical efficacy. It should be noted that the patient identification used in these data sets was inconsistent. In some of the data sets the identification utilized the nomenclature of Warner Lambert and in other cases that of iBRD was employed. This is a potential source of error in evaluation of the data sets, and to a lesser extent the NDA.

3.1 Chemistry:

3.2 Name:
Zonisamide

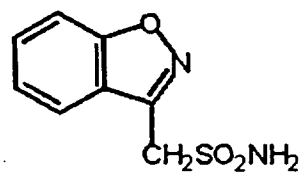
3.3 Chemical Name:
1,2-benzisoxazole-3-methanesulfonamide

3.4 Molecular Formula:
$C_8H_8N_2O_3S$

3.5 Molecular Weight:
212.23

3.6 Structure:

Figure 1



3.7 Drug Category:

3.8 Forms available for Proposed Study:
Zonisamide 100 mg Capsules

4. Pharmacology:
The exact method of action for zonisamide is unknown. In *in vitro* studies, zonisamide blocks sodium channels and reduces the voltage-dependent transient inward currents, with resulting stabilization of neuronal membranes and suppression of neuronal hypersynchrony. In animal models of epilepsy, zonisamide has been shown to prevent seizure spread in the maximum electroshock (MES) model. In contrast zonisamide did not block the seizures induced by pentylenetetrazol. In the anticonvulsant kindling screen, zonisamide elevated the seizure threshold. Zonisamide suppresses interictal spikes and seizure activity in animal models (tungstic acid and cortical freezing). Zonisamide also supressed generalized seizures induced by tungstic acid application to the thalamus.

5. Toxicology:

5.1 Animal Toxicology:

A brief summary of positive findings is listed below. These findings will be discussed in detail by the Pharmacology reviewer.

5.1.1 Hepatic:

In the rat multiple-dose toxicology studies, at zonisamide doses of 100 - 200 mg/kg/day, increases in alkaline phosphatase, GPT, and liver weights were observed. There were no histopathologic correlates to these changes. The parameters returned to baseline following discontinuation of zonisamide. In the dog 52 week studies, doses of 75 mg/kg/day resulted in liver enlargement and increased liver weights. Again, there was no histopathologic evidence of heaptic damage.

5.1.2 Renal:

In the rat multiple-dose toxicology studies, at zonisamide doses of 100 - 200 mg/kg/day, increases in urea nitrogen, sodium, potassium, phosphorus, urine output and kidney weights were seen. An elevation in urea nitrogen was also observed in rats after 12 months of treatment with zonisamide at lower doses (20mg/kg/day). There were no histopathologic correlates to these changes. The parameters returned to baseline following discontinuation of zonisamide. Necropsy findings revealed renal stones with an incidence of 4/20 in males and 1/20 in females at 200 mg/kg/day.

5.2 Teratogenicity

Teratology studies indicate zonisamide is not teratogenic at doses of 250 mg/kg in the mouse, 40 mg/kg in the rat, 10 mg/kg in the dog, and 20 mg/kg in the monkey. However, zonisamide has produced teratogenic effects at higher doses in all species except the monkey. In the dog reduced fetal weights were seen at a dose of ≥30 mg/kg of zonisamide. Fetal deaths occurred at a dose of 60 mg/kg, and malformations of soft tissue and skeletal structures were observed. In the monkey, spontaneous abortions occurred at doses of 10 and 20 mg/kg.

5.3 Miscellaneous

Zonisamide was not genotoxic in a battery of mutagenicity tests.

6. Human Pharmacokinetics:

The following is a brief summary of the pharmakokinetica and bioavailability of zonisamide. Additional information will be provided by the Biopharmaceutics reviewer.

6.1 General Pharmacokinetics:

The general pharmacokinetics (absorption, distribution, metabolism, and elimination / excretion) of zonisamide in healthy subjects following single and multiple doses are presented in Table 25. Following multiple doses of 400 mg (administered as 200 mg po BID), the C_{max}, T_{max}, and $T_{1/2}$ are 28 ug/ml, 2.1 hours and 68.6 hours, respectively.

6.2 Concomitant AEDs:

Animal and clinical studies suggest that Zonisamide does not have significant effects on the plasma levels of concomitant AEDs. In contrast, phenytoin, carbamazepine, phenobarbital, and valproic acid shorten the half life of zonisamide. Absorption (C_{max} and T_{max}) of zonisamide is not affected by concomitant AEDs.

7. Previous Human Experience:

Marketing applications have only been submitted in Japan and Korea, and both were approved. Zonisamide (Excergran ® tablets 100 mg and powder) has been marketed in Japan since 1989. In Korea, zonisamide has been marketed as Dong-A Excegran ® tablets since 1992. Zonisamide has not been withdrawn from the market in any country. Approval has not been refused in any country on the basis of safety issues. There are no countries where approval is pending.

8. Efficacy Studies:

8.1 Overview of Efficacy Studies

The sponsor has submitted three double-blind, randomized, placebo controlled multi-center studies in support of an efficacy claim (Table 1). Two of the studies 912-US and 912-EUR were sponsored by [redacted] The third study, 810-922 (922-US), was sponsored by [redacted] The sponsor considered the two US studies 912-US and 922-US to be the pivotal studies. They initially proposed not to include 912-EUR since they believed that it did not meet good clinical practice requirements. At the agency's request the sponsor has submitted the results of that study for review. This efficacy review will focus on these three studies.

Table 1

Placebo-Controlled Studies Placebo-Controlled Studies					
Protocol Designation/ NDA Report No.	**Zonisamide (no. of pts)**	**Placebo (no. of pts)**	**Duration (weeks)**	**Dosage (mg/ day)**	**Extension Phase (Protocol Designation)**
810-922/ [redacted]922	118	85	20	400	Yes (ongoing)
912-US/	78	74	12	400- 900 *	Yes

720- 02266- 96					(720- 02266- 96- Ext)
912-EUR/ 720- 02275- 96	73	71	12	400-1000*	Yes (720- 02275- 96- Ext)
Modified from the sponsor's submission. * Maximum dosage in the controlled portion of the study.					

8.2 Summary of Individual Efficacy Studies:

8.2.1 Study: 912-US

8.2.1.1 Title:

A Multi-center Placebo-controlled Double-blind Study to Determine the Efficacy and Safety of Zonisamide (CI-912) in the Treatment of Complex Partial Seizures in Medically Refractory Patients

8.2.1.2 Objective / Rationale:

The objectives of this study were to evaluate the safety and efficacy of a range of doses of zonisamide as adjunctive therapy in medically refractory patients receiving other anti-epileptic medications (AEDs) and to determine the plasma levels of zonisamide when administered at therapeutic doses. In addition, the safety of the was evaluated by comparing the frequency and severity of side effects with zonisamide or placebo.

8.2.1.3 Study Design:

The study was a multi-center, outpatient, parallel group, double-blind, randomized, placebo-controlled study of zonisamide as adjunctive therapy in the treatment of medically refractory subjects with complex partial seizures.

8.2.1.3.1 Study Dates:

August 24, 1983 to July 23, 1986

8.2.1.3.2 Inclusion Criteria:

- Subjects will be adult male or female seizure patients between the ages of 18 and 59. Female seizure patients, if of child-bearing potential, must not be pregnant or nursing and must agree to practice during the study a reliable form of contraception (oral contraceptive, condom, intrauterine device, or diaphragm).
- During the four months preceding the study, patients must be averaging **at least four complex partial seizures per month.** Such patients may also have simple partial seizures and, while awake, during the four months preceding the study, up to eight primary or secondary generalized tonic, clonic, or tonic-clonic seizures. For generalized seizures of these types occurring during sleep, no upper limit on the number of seizures is specified.
- Current antiepileptic therapy must include a combination of one to two of phenytoin, carbamazepine, and phenobarbital or primidone. The subjects must be considered by their neurologist to be treatment failures, not failures in terms of treatment compliance, or failure to

achieve therapeutic plasma levels of the antiepileptic drugs. In order to insure uniform therapy, the antiepileptic drugs will be prescribed by brand name.
- Patients must be able to count their seizures.

8.2.1.3.3 Exclusion Criteria:

- Patients with a history or evidence of a progressive structural lesion in the CNS, a progressive encephalopathy, or of clinically significant organic disease, including chronic cardiac, hematological, hepatic, or renal disease, or progressive ophthalmologic disease.
- Patients having a history of the occurrence of more than eight generalized seizures, other than those occurring during sleep, in the four months prior to the study.
- Patients having generalized seizures of types other than those listed in the inclusion criteria, such as myoclonic, atonic, and absence seizures.
- Female patients who are pregnant or nursing.
- Female patients of childbearing potential who are not deemed to be reliable in regard to practicing a reliable form of contraception.
- Patients with significant mental retardation.
- Any predisposing condition that might interfere with the absorption, distribution, and/or excretion of drugs.
- Patients chronically (> ten days) taking psychotropic or other medication considered by the investigator to have the potential to interfere with the results of the study.
- Since CI-912 (zonisamide) has a sulfonamide structure, patients known to have a deficiency of glucose-6phasphate dehydrogenase or subjects with a history of hemolytic anemia or acute intermittent porphyria.
- Patients with a history of sensitivity to sulfonamide drugs.
- Patients with a history of chronic excessive alcohol consumption or drug abuse should be excluded.
- Patients with clinical laboratory determinations outside of an acceptable range should be excluded unless the finding can be attributed to current AED therapy.
- Any patient not reasonably expected to complete the trial.

8.2.1.3.4 Seizure Data

The International Classification of Epileptic Seizures was used to classify the patient's seizures. At each clinic visit, the investigator reviewed the seizure record and recorded the date, number, duration, and type of seizures. The following types of seizures were used: simple partial (SP), complex partial moderate (CPM), complex partial severe (CPS), generalized tonic-clonic awake (G1), generalized tonic-clonic asleep (G2), others, and flurries (defined as ten or more seizures which occurred so closely together that the patient was unable to determine the end of one seizure and the beginning of the next, and thus was unable to count the actual number of seizures which occurred). The sponsor states in inclusion criteria section of the study report that "No distinction was made between those generalized tonic-clonic seizures which appeared to be primary or were secondarily generalized." It is not clear from the reports if this strategy was also employed when recording the seizure data. A review of the seizure database suggests that the number of G1 and G2 seizures was small and would not affect the analysis.

8.2.1.3.5 Phases of Study:

The study consists of six phases. The first phase consists of a 8 - 12 week baseline phase during which the subjects receive treatment with one to two of phenytoin, carbamazepine, and phenobarbital or primidone. The second phase is a 12 week double-blind comparison of the addition of zonisamide or placebo to treatment. The third phase consists of breaking the code, evaluation of treatment and assignment of further treatment. The fourth phase consists of a crossover from placebo to zonisamide. The fourth phase has a duration of 12 weeks. The fifth phase consist of continued treatment with zonisamide for subjects receiving therapeutic benefit. The sixth phase consists of a 6 week follow-up of subjects not continuing treatment with zonisamide.

8.2.1.3.6 Dosing with Placebo or Zonisamide:

The study drug will be given q 12 hours. The zonisamide dose will be calculated to give a plasma trough level of between 20 and 30 ug/ml, with the initial dose of 7 mg/kg/day, in the following ranges based on body weight in kg: ≤ 60 kg - 400 mg, 61 - 70 kg - 500 mg, and > 70 kg - 600 mg. The dose of zonisamide was evaluated by a second investigator not blinded to the treatment based on side effects and seizure control. The dose of zonisamide could have been increased to a maximum dose of 20 mg/kg or a trough level of 40 ug/ml. Random changes in the placebo doses were made during the study.

8.2.1.3.7 Protocol Amendments:

During the course of this study, the sponsor submitted nine protocol amendments.

8.2.1.3.7.1 Amendment 1, Effective Date: May 14, 1984.

This amendment increased the number of subjects per treatment center from 10 - 20 to 20 - 30. This change was based on the sponsors ability to enter subjects at a faster rate than initially planned.

8.2.1.3.7.2 Amendment 2, Effective Date: June 1, 1984

The sponsor reported that in patients receiving zonisamide during the 12-week double-blind period, there was a marked reduction in the frequency of complex partial seizures at doses not causing unacceptable side effects. In addition, clinical laboratory monitoring including hematologic, hepatic, and renal function did not reveal any abnormalities. Based on this information, this amendment extended the period of treatment with zonisamide an additional 9 months, for a total of 12 months.

8.2.1.3.7.3 Amendment 3, Effective Date: July 9, 1984

A preliminary analysis indicated that fewer side effects were experienced if zonisamide was introduced to treatment at a sub-therapeutic dose and then gradually increased to a therapeutic level. The initial dose was changed to 1.5 mg/kg and titrated to 7 mg/kg over the following 28 days.

Amendment 4, Effective Date: July 24, 1984

The sponsor reported that in patients receiving zonisamide during the 12-week double-blind period, there was a marked reduction in the frequency of complex partial seizures at doses not causing unacceptable side effects. In addition, clinical laboratory monitoring including hematologic, hepatic, and renal function did not reveal any abnormalities. Based on this information, this amendment extended the period of treatment with zonisamide an additional 6 months, for a total of 18 months.

Amendment 5, Effective Date: September 1, 1984
This amendment increased the number of subjects per center to 30 - 40. The sponsor argued that since patients entering the study have continued to receive therapeutic benefit from treatment with zonisamide, it is appropriate to increase further the number of patients to be studied to a total of 30 to 40.

Amendment 6, Effective Date: October 15, 1984
This amendment added the determination of elimination half-life of zonisamide after chronic administration.

Amendment 7, Effective Date: March 25, 1985
Amended the age range from 18-59 to 18-65.

Amendment 8, Effective Date: May 1, 1985
This amendment extended the treatment with zonisamide until the drug is commercially available or the IND is withdrawn.

Amendment 9, Effective Date: August 13, 1985
Duplicate of amendment 5.

8.2.1.4 Demographics:

One hundred and fifty-two subjects were enrolled in this study with 78 subjects being randomized to receive zonisamide and 74 to receive placebo. The demographics are summarized in Table 2. The demographic characteristics of the two groups were balanced except for a higher percentage of females enrolled in the placebo group compared to zonisamide.

Table 2

Patient Demographic and Pre-study Seizure Characteristics (Protocol 912-US)		
Demography Characteristic	Zonisamide (N = 78)	Placebo (N = 74)
Gender [a] N (%)		
Male	58 (74.4)	43 (58.1)
Female	20 (25.6)	31 (41.9)
Race N (%)		
Caucasian	68 (87.2)	64 (86.5)
Black	4 (5.1)	5 (6.8)
Other [b]	6 (7.7)	5 (6.8)
Age (yr)		
<40	57 (73.1)	49 (66.2)
≥40- <65	21 (26.9)	23 (31.1)
≥65	0 (0.0)	2 (2.7)
Mean ± SD	35.6± 12.1	36.4± 11.3
Range	17.9- 64.1	17.8- 67.5
Weight (kg)		
Mean ± SD	74.8± 15.7	72.8± 16.1
Range	44.2- 114.1	40.9- 120.0
Height (cm)		
Mean ± SD	173.0± 9.7	171.0± 11.9
Range	147.0- 195.6	140.0- 195.6
Pre-study Monthly Seizure Activity (4 months before baseline) All Partial (Complex + Simple)		
Mean	21.7	18.3
Median	7.5	11.1
Range	[redacted]	[redacted]
Complex Partial		
Mean	19.5	12.4
Median	7.0	7.8
Range	[redacted]	[redacted]
Other Types (Including Generalized)		
Mean	0.3	2.2
Median	0.0	0.0
Range	[redacted]	[redacted]

a Statistical difference between treatment groups ($p<0.05$).
b Other included Hispanic.
Reference: Appendices B.1; C.4.1, C.4.2, C.5.

Taken from the sponsor's submission.

8.2.1.5 Concomitant Antiepileptic Drugs:

The concomitant AEDs used during the course of this study (baseline and treatment) are presented in Table 3.

Table 3

Summary of Concurrent Antiepileptic Drugs (Protocol 912-US)

	Zonisamide (N= 78)				Placebo (N= 74)			
	Baseline		Treatment		Baseline		Treatment	
Medications	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**
Carbamazepine + Phenytoin	36	46.2	37	47.4	29	39.2	29	39.2
Carbamazepine	14	17.9	13	16.7	16	21.6	17	23.0
Phenytoin	12	15.4	11	14.1	6	8.1	6	8.1
Carbamazepine + Primidone	4	5.1	4	5.1	5	6.8	5	6.8
Phenytoin + Phenobarbital	2	2.6	3	3.8	3	4.1	3	4.1
Primidone	2	2.6	2	2.6	1	1.4	0	0.0
Phenytoin + Primidone	2	2.6	2	2.6	2	2.7	1	1.4
Phenobarbital	1	1.3	1	1.3	0	0.0	0	0.0
Carbamazepine + Phenobarbital	1	1.3	1	1.3	5	6.8	5	6.8
Other drugs and combinations	4	5.1	4	5.1	7	9.5	8	10.8

Reference: Appendices B.8, B.9; C.12, C.13.

Reproduced from the sponsor's submission.

8.2.1.6 Conduct of Study:

8.2.1.6.1 Investigators / Location:

This study was conducted at four sites in the United States. The distribution of subjects per site is listed in Table 4.

Table 4

Number of Patients Randomized to Each Treatment Group by Study Center and Investigator(s) (Protocol 912-US)

Study Center	Investigator(s) (Location)	Patients Enrolled in Baseline	Patients Not Randomized	Zonisamide	Placebo	Total
912- 12	R Ramsay/ A Guterman (Miami, FL)	31	0	16	15	31
912- 13	J Sackellares/ P Donofrio (Ann Arbor, MI)	43	0	22	21	43
912- 15	B Wilder (Gainesville, FL)	44	0	22	22	44
912- 21	T Browne/ G Howard (Boston, MA)	34	0	18	16	34

* Study center number also identifies the investigator(s) and protocol numbers.
Reference: Appendix B.2.
Taken from the sponsor's submission.

8.2.1.6.2 Patient Disposition:

One hundred and fifty-two subjects entered the study, with a combined completion rate of approx. 85%. Approximately 20% of the subjects in the zonisamide group and 10% in the placebo group discontinued the study. The major reason for discontinuation in the zonisamide group was adverse events and in the placebo group was lack of efficacy. Approximately half of the subjects who withdrew from the zonisamide group due to adverse events did so in the first four weeks. Six of the subjects who withdrew due to adverse events were started on the initial dose of 7 mg/kg/day, prior to the protocol amendment which allowed for a titration to the desired dose. The disposition of subjects is summarized in Table 5.

Table 5

Summary of Patient Disposition
(Protocol 912-US)

	Zonisamide (N = 78)		**Placebo (N= 74)**		**All Patients (N = 152)**	
Reason	N	%	N	%	N	%
Study completed	62	79.5	67	90.5	129	84.9
Study discontinued	16	20.5	7	9.5	23	15.1
Lack of efficacy	0	0.0	4	5.4	4	2.6
Adverse event	12	15.4	1	1.4	13	8.6
Death	0	0.0	1	1.4	1	0.7
Other *	4	5.1	1	1.4	5	3.3

* Other included personal reasons, study discontinued by sponsor, or reason unknown.
Reference: Appendices B.3; C.9, C.10, C.24.
Taken from the sponsor's submission.

8.2.1.6.3 Dosing:

The dosing of Zonisamide in this study ranged from 100 - 1200 mg/day. During the controlled phase of this study, the dose range was from 100 to 900 mg/day.

8.2.1.6.4 Protocol Deviations:

The protocol deviations are summarized in Table 6. The most notable protocol deviations were for concomitant AEDs not specified in the protocol, with nine zonisamide subjects and four placebo subjects in this category. In addition, 8 subjects in the zonisamide group and four in the placebo group had less than the protocol specified minimum of 4 complex partial seizures / month in the four months preceding the study.

Table 6

Protocol Deviations for Study 912-US			
Deviation	**Zonisamide**	**Placebo**	**Comments**
Less than 4 CP/ mo during 4 months prior to a study	8	4	Nine of these deviations were at site 912-12
Myoclonic seizures during baseline	0	2	
Concomitant treatment with valproic acid or the combination of valproic acid and sodium valproate	1	4	All of these deviations were at site 912-15
Concomitant treatment with diazepam	1	0	
Concomitant treatment with mephobarbital	2	0	
Concomitant treatment with Tranxene® (clorazepate)	5	0	
Greater than 65 years of age	0	2	
Less than 18 years of age	1	1	
History of alcohol abuse	1	0	

8.2.1.7 Primary Efficacy Measure:

The protocol defined primary efficacy measure was "the type, frequency, and duration of seizures during treatment with zonisamide plus phenytoin, carbamazepine, and phenobarbital or primidone". The efficacy criteria used in the actual evaluation by the sponsor was a reduction from baseline in the frequency of all partial seizures. This was measured by the median percent change in seizure frequency between Weeks 5 to 12.

8.2.1.8 Analysis Plan:

Based on a pre-NDA meeting with Dr. Todd Sahlroot and Dr. David Hoberman (March 19, 1996), four patient populations were agreed on for the analysis of the primary efficacy parameter.

- Population 1: The primary efficacy analysis population defined as intent-to-treat patients having received at least one dose of study drug (zonisamide or placebo) during the double-blind phase (Weeks 5 through 12) without the use of imputed seizure rate values. If a patient withdrew during the 4-week dose introduction phase, then that patient was excluded from this population.
- Population 2: In this analysis, the percentage change in seizure frequency was analyzed using the intent-to-treat population for Weeks 5 through 12. For those patients who withdrew during the 4-week dose introduction phase, the maximum percent increase for their respective treatment group was imputed.

This evaluation evaluates the impact of premature withdrawals on the efficacy data.

- Population 3: Intent-to-treat defined as using all post-randomization data with no imputation.
- Population 4: Efficacy evaluable which included patients who had to receive at least 56 days of treatment with other antiepileptic medications during the baseline phase and at least 14 days of treatment with study medication after the 4- week dose-introduction phase. In addition, patients had to have an average of at least two CP/28 days at baseline for the CP comparisons and two of either kind for the CP+SP comparison. Data from the dose introduction phase were not included.

Baseline comparability (baseline seizure frequency, age, weight, duration of epilepsy, and seizure rates at screening) was assessed using the Wilcoxon Two-Sample Test. Comparability with respect to gender, age group, and race was evaluated using Pearson's Chi-square Test.

8.2.1.9 Primary Efficacy Analysis:

Analysis of the primary outcome measure for study 912-US, for each of the four populations previously described is presented in Table 7. There was a statistically significant reduction from baseline seizure frequency (all partial seizures) when zonisamide was compared to placebo. The intent-to-treat analysis without imputation is highlighted in gray.

Table 7

Reduction From Baseline in the Frequency of All Partial Seizures for Study 912-US

	Zonisamide		Placebo		
Population	N	Median % Change	N	Median % Change	p- value
1 [b]	69	-29.5 [a]	72	1.8	0.0004
2 [c]	78	-22.9 [a]	74	4.6	0.0342
3 [d]	78	-25.4 [a]	74	2.2	0.0003
4 [e]	66	-30.1 [a]	71	3.0	0.0001

a Significantly greater reduction than placebo ($p \leq 0.05$)
b Intent-to-treat using data from last 8 weeks of the double-blind phase; patients not completing the 4-week dose introduction phase are excluded (Population 1).
c Same as intent-to-treat population but includes patients who dropped during dose introduction phase (includes imputation for patients not completing the dose introduction phase).
d Intent-to-treat using all post-randomization data with no imputation.
e Efficacy evaluable population.

Reference: Appendices B.13; C.6.
Reproduced from the sponsor's submission.

8.2.1.10 Secondary Efficacy Measures:

The proportion of patients with a ≥ 50% reduction in seizure frequency when the frequency during treatment was compared with baseline frequency for a given patient was a secondary efficacy measure.

8.2.1.11 Secondary Efficacy Analysis:

Analysis of the secondary outcome measure for study 912-US, for each of the four populations previously described is presented in Table 8. There was a statistically significant higher proportion of responders when zonisamide was compared to placebo, with the intent-to-treat analysis without imputation (highlighted in gray in Table 8). Analysis using the other three populations failed to reach statistical significance. Table 9 shows the analysis of the secondary outcome measure for all partial seizures, complex partial seizures and all seizures using an intent-to-treat population.

Table 8

Proportion Of Patients With ≥ 50% Reduction In Seizure Frequency From Baseline

	Zonisamide		Placebo		
Population	N	%	N	%	p- value
1 [b]	18	26.1	12	16.7	0.08
2 [c]	18	23.1	12	16.7	0.08
3 [d]	19	24.4	9	12.2	0.016
4 [e]	18	27.3	12	16.9	0.068

a Significantly greater reduction than placebo (p≤0.05)
b Intent-to-treat using data from last 8 weeks of the double-blind phase: patients not completing the 4-week dose introduction phase are excluded (Population 1).
c Same as intent-to-treat population but includes patients who dropped during dose introduction phase (includes imputation for patients not completing the dose introduction phase).
d Intent-to-treat using all post-randomization data with no imputation.
e Efficacy evaluable population.

Table 9

Proportion Of Patients With ≥ 50% Reduction In Seizure Frequency From Baseline*

	Zonisamide		Placebo		
Population	**N**	**(%)**	**N**	**(%)**	**p value**
All Partial Seizures	19	24.4	9	12.2	0.016
Complex Partial Seizures	22	28.2	8	11.1	0.010
All Seizures	19	24.4	7	9.5	0.016

* Intent-to-treat using all post-randomization data with no imputation.

8.2.1.12 The Role of Concomitant AEDs:

The role of concomitant AEDs in the efficacy of zonisamide was evaluated by examining the dose increases and decreases and the plasma levels during the controlled portion of this study.

There was no statistical difference in the number of subjects that had at least one dose increase of their concomitant AEDs, 9 subjects (12.3%) and 14 (17.95%) in the placebo and zonisamide groups, respectively (Figure 5). In contrast, there was a statistically significant difference between the number of subjects with at least one dose decrease in the two groups, with 10 subjects (13.70%) and 27 (34.62%) in the placebo and zonisamide groups, respectively (Figure 6). There was no difference in the number of dose increases in the two groups. In contrast, there was a statistically significant greater number of dose decreases in the zonisamide group (Figure 7). A statistically significant difference in the number of dose decreases was seen for carbamazepine and phenytoin, but not for the other AEDs (Figure 8 - Figure 12). These changes would have the tendency to favor placebo over zonisamide unless zonisamide.

In examining the plasma levels of concomitant AEDs during the controlled portion of the study, only one AED, primidone, showed a change, with an increase in levels in the zonisamide group (Figure 13 - Figure 24). Of note, eleven (11) subjects in the placebo group had zonisamide plasma levels > 0, with a range of 0.342 - 8.8 ug/ml (Table 26) during the controlled portion of the study. It is not clear, if this represents dosing errors or a problem with the assay. Neither of the other two studies (see below) had a similar finding. If this represents dosing errors, it would tend to favor placebo over zonisamide in the efficacy evaluation, but could potentially favor zonisamide in the safety analysis.

8.2.1.13 Concomitant Non-AED Medications:

A review of the concomitant non-AED medications revealed that 3 subjects in the placebo group and 9 subjects in the zonisamide group received "non-AEDs" with possible AED properties during the controlled portion of the study. These medications included diazepam, lorazepam, tranxene, xanax, halcion, and diamox. Five of the nine subjects in the zonisamide group were receiving the medication at baseline as well (see protocol deviations).

8.2.1.14 Dosage of Study Medication:

In contrast to the more recent US study (922-US) to be discussed later, the dose zonisamide could be adjusted based on adverse events and seizure control (max. trough plasma level of 40 ug/ml or a max. dose of 20 mg/kg). Doses up to 900 mg were utilized during the controlled portion of the study. In an attempt to evaluate the role of higher doses (> 400 mg) in the efficacy of zonisamide, both the placebo and zonisamide groups were categorized as low dose (≤ 400 mg) or high dose (>400 mg) based on the highest dose received during the controlled phase of the study. The results of that analysis are presented in Table 10. This

descriptive analysis without a statistical evaluation suggests that both the low dose and high dose zonisamide groups had a similar reduction in the seizure rate.

Table 10

Comparison of Efficacy for Low Dose vs. High Dose [a] in 912-US			
Treatment Group	**Dose Class [a]**	**N**	**Median [b]**
Placebo	0	9	-58.7
Zonisamide	0	26	-27.1
Placebo	1	65	6.1
Zonisamide	1	52	-30.6

[a] Max. dose during the controlled portion of the study 0 = ≤ 400 mg; 1 = > 400 mg
[b] Median Pct. Change in 28-day rate, weeks 5 to 12

8.2.1.15 Plasma Levels of Zonisamide

During the controlled portion of the trial, the zonisamide levels ranged from 0 - 40.4, with the maximum level occurring with a dose of 500 mg / day (Figure 3). The maximum plasma levels during trial, including the open-label extension, ranged from 0 - 69.0, with the maximum level occurring at a dose of 900 mg / day (Figure 4).

8.2.1.16 Study 912-US Conclusions:

The results of this study support zonisamide as an effective add-on treatment in patients with partial seizures and partial seizures with secondary generalization. The use of other concomitant antiepilepsy drugs (AEDs) did not appear to affect the outcome of this study. The use of concomitant AEDs was approximately equal in the two groups, placebo and zonisamide. There number of concmitant AED dose decreases was greater in the zonisamide group, which would tend to favor placebo over zonisamide. In addition, the plasma levels of the concomitant AEDs remained relatively constant during the controlled portion of the study. Finally, the number of subjects in the two groups who received "non-AED" medications with possible AED effects was comparable, if the subjects taking the medication at baseline are excluded.

8.2.2 Study: 912-EUR

8.2.2.1 Title:

A multicenter placebo-controlled double-blind study to determine the efficacy and safety of zonisamide (CI-912) in the treatment of complex partial seizures in medically refractory patients (EUR)

8.2.2.2 Design:

The design of this study of this study, including objectives, inclusion / exclusion criteria, and phases were identical to those for study 912-US, and have been

described above. In the 912-US study the dosing was BID and in the 912-EUR study the dosing was once a day. Amendments to this protocol were similar in nature and time course to those listed for 912-US and will not be reviewed again.

8.2.2.3 Study Dates:

June 25, 1984 to October 7, 1986.

8.2.2.4 Demographics:

The sponsor's summary table is reproduced in Table 11. The baseline characteristics were balanced across treatment groups in this study. The treatment groups were not statistically significantly different at screening with regard to pre-study seizure frequency for all partial, complex partial, and all seizures (p=0.687, 0.671, 0.441, respectively).

Table 11

Demographic and Baseline Seizure Characteristics for Study 912-EUR		
	Zonisamide (N = 73)	Placebo (N = 71)
Demography Characteristic		
Gender N (%)		
Male	43 (58.9)	42 (59.2)
Female	30 (41.1)	29 (40.8)
Race N (%)		
Caucasian	73 (100.0)	71 (100.0)
Age (yr)		
<40 yrs	52 (71.2)	48 (67.6)
≥40 yrs, <65 yrs	21 (28.8)	23 (32.4)
≥65 yrs	0 (0.0)	0 (0.0)
Mean ± SD	35.4± 10.9	33.9± 11.8
Range	17.4 - 60.9	18.5 - 60.2
Weight (kg)		
Mean± SD	66.7± 10.9	65.7± 10.3
Range	45.0 - 103.0	43.0- 96.0
Height (cm)		
Mean± SD	168.4± 8.4	168.1± 9.9
Range	147.0 - 187.0	125.0 - 190.0
Pre-study Monthly Seizure Activity (4 months before baseline)		
All Partial (Complex + Simple Partial)		
Mean	29.7	24.0
Median	11.3	11.0
Range	[redacted]	[redacted]
Complex Partial		
Mean	28.5	20.5
Median	10.0	10.0
Range	[redacted]	[redacted]
Other (Including Generalized)		
Mean	0.5	0.4
Median	0	0
Range	[redacted]	[redacted]

8.2.2.5 Concomitant Antiepileptic Drugs:

Table 12 shows the summary of concomitant AEDs used during the course of this study 912-EUR.

Table 12

Summary of Concurrent Antiepileptic Medications for Study 912-EUR								
	Zonisamide (N=73)				Placebo (N=71)			
	Baseline		Treatment		Baseline		Treatment	
Medications	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**
Carbamazepine	10	13.7	13	17.8	15	21.1	16	22.5
Phenytoin + Phenobarbital	7	9.6	11	15.1	8	11.3	10	14.1
Carbamazepine + Primidone	6	8.2	8	11.0	5	7.0	3	4.2
Carbamazepine + Phenobarbital	5	6.8	6	8.2	5	7.0	6	8.5
Phenytoin	5	6.8	4	5.5	3	4.2	3	4.2
Carbamazepine + Phenytoin	4	5.5	3	4.1	8	11.3	11	15.5
Phenobarbital	2	2.7	3	4.1	3	4.2	3	4.2
Primidone	2	2.7	2	2.7	1	1.4	1	1.4
Phenytoin + Primidone	1	1.4	2	2.7	3	4.2	3	4.2
Valproic Acid + Carbamazepine	2	2.7	2	2.7	2	2.8	2	2.8
Valproic Acid	1	1.4	1	1.4	0	0.0	0	0.0
Valproic Acid + Phenytoin	0	0.0	1	1.4	0	0.0	0	0.0
Valproic Acid + Primidone	0	0.0	0	0.0	1	1.4	1	1.4
Other Drugs and Combinations	15	20.5	17	23.3	10	14.1	12	16.9
No Information	13	17.8	0	0.0	7	9.9	0	0.0

Reference: Appendices B.8, B.9; C.12, C.13.
Reproduced from the sponsor's submission.

8.2.2.6 Conduct of Study:

8.2.2.6.1 Investigators / Location:

This study was a multi-center study conducted at 10 sites in Europe. The number of subjects randomized by study site and investigator is summarized in Table 13.

Table 13

Number of Patients Randomized to Each Treatment Group by Study Site and Investigator					
Study site	**Investigator(s) (location)**	**Patients Enrolled in Baseline**	**Zonisamide**	**Placebo**	**Total**
912- 27(MUN/ 642)	D Schmidt MD Berlin, W. Germany	3	2	1	3
912- 28(PAR/ 31)	P Loiseau MD Bordeaux, France	29	14	15	29
912- 29(MUN/ 646)	E Deisenhammer MD Linz, Austria	11	5	6	11
912- 30(MUN/ 647)	PA Despland MD Lausanne, Switzerland	9	5	4	9

912- 31(MUN/ 648)	M Elgi MD Zurich, Switzerland	17	9	8	17
912- 32(MUN/ 645)	G Bauer MD Innsbruck, Austria	23	12	11	23
912- 33(MUN/ 651)	E Stenzel MD Bielefeld, W. Germany	8	4	4	8
912-35(MUN/653)	V Blankenhorn MD Kehl-Kork, W. Germany	30	15	15	30
912-36(MAD/103)	JH Perez MD Madrid, Spain	4	2	2	4
912-48(MUN/659)	D Klinger MD Linz, Austria	10	5	5	10

Taken from the sponsor's submission.

8.2.2.6.2 Patient Disposition:

One hundred and forty-four (144) subjects were enrolled in the baseline phase of this study at 10 sites. The patient disposition for this study is summarized in Table 14. Ninety per cent of the subjects completed the double-blind portion of the study. Twelve (16%) of zonisamide patients and three (4%) placebo patients withdrew from the trial prematurely.

Table 14

Summary of Patient Disposition in Study 912-EUR

	Zonisamide		Placebo		All	
Reason	**N**	**%**	**N**	**%**	**N**	**%**
Study completed	61	83.6	68	95.8	129	89.6
Study discontinued	12	16.4	3	4.2	15	10.4
Lack of efficacy	4	5.5	0	0	4	2.8
Adverse event	5	6.8	1	1.4	6	4.2
Other [a]	3	4.1	2	2.8	5	3.5

[a] Other included personal reasons, study discontinued by sponsor, seizure
Reproduced from the sponsor's submission.

8.2.2.7 Primary Efficacy Measure:

The protocol defined primary efficacy measure was "the type, frequency, and duration of seizures during treatment with zonisamide plus phenytoin, carbamazepine, and phenobarbital or primidone". The efficacy criteria used in the actual evaluation by the sponsor was a reduction from baseline in the frequency of all partial seizures. This was measured by the median percent change in seizure frequency between Weeks 5 to 12. The populations analyzed are identical to those presented above for 912-US.

8.2.2.8 Primary Efficacy Analysis:

Table 15 shows the results of efficacy analysis for the primary outcome measure (all partial seizures) for the four populations described above. This study failed to show statistical significance using the primary outcome measure for all partial seizures in an intent-to-treat population. Likewise, similar analyses for complex partial seizures and for all seizures, including generalized seizures, failed to reach statistical significance in the intent-to-treat population.

Table 15

Reduction From Baseline in the Frequency of All Partial Seizures for Study 912-EUR

	Zonisamide		Placebo		
Population	N	Median % Change	N	Median % Change	p-value
1 [b]	69	-20.0	70	0.3	0.210
2 [c]	72	-17.5	71	4.5	0.234
3 [d]	72	-24.8	71	2.9	0.117
4 [e]	65	-20.5 [a]	67	4.5	0.041

a Significantly greater reduction than placebo (p≤0.05)
b Intent-to-treat using data from last 8 weeks of the double-blind phase; patients not completing the 4-week dose introduction phase are excluded (Population 1).
c Same as intent-to-treat population but includes patients who dropped during dose introduction phase (includes imputation for patients not completing the dose introduction phase).
d Intent-to-treat using all post-randomization data with no imputation.
e Efficacy evaluable population.

Reference: Appendices B.13; C.6.
Reproduced from the sponsor's submission.

8.2.2.9 Secondary Efficacy Measures:

The proportion of patients with a ≥ 50% reduction in seizure frequency when the frequency during treatment was compared with baseline frequency for a given patient was a secondary efficacy measure.

8.2.2.10 Secondary Efficacy Analysis:-

The analyses of the secondary outcome measure utilizing the previously described subject populations are shown in

Table 16. This study failed to reach statistical significance with respect to the secondary outcome using an intent-to-treat population without imputation. Table 17 shows the analysis of the secondary outcome measure for all partial seizures, complex partial seizures and all seizures using an intent-to-treat population. Likewise statistical significance was not obtained for any of the sub-groups.

Table 16

Proportion Of Patients With ≥ 50% Reduction In Seizure Frequency (All Partial) From Baseline					
	Zonisamide		Placebo		
Population	N	%	N	%	p- value
1 [b]	17	24.6	8	11.4	0.047
2 [c]	17	23.6	8	11.3	0.047
3 [d]	18	25.0	10	14.1	0.103
4 [e]	17	26.2	7	10.4	0.024

a Significantly greater reduction than placebo ($p \leq 0.05$)
b Intent-to-treat using data from last 8 weeks of the double-blind phase; patients not completing the 4-week dose introduction phase are excluded (Population 1).
c Same as intent-to-treat population but includes patients who dropped during dose introduction phase (includes imputation for patients not completing the dose introduction phase).
d Intent-to-treat using all post-randomization data with no imputation.
e Efficacy evaluable population.

Reference: Appendices B.13; C.6.
Reproduced from the sponsor's submission.

Table 17

Proportion Of Patients With ≥ 50% Reduction In Seizure Frequency From Baseline *					
	Zonisamide		Placebo		
Population	N	(%)	N	(%)	p value
All Partial Seizures	18	25.0	10	14.1	0.103
Complex Partial Seizures	19	26.4	12	16.9	0.173
All Seizures	17	23.6	9	12.7	0.105

* Intent-to-treat using all post-randomization data with no imputation.

8.2.2.11 The Role of Concomitant AEDs:

The role of concomitant AEDs in the efficacy of zonisamide was evaluated by examining the dose increases and decreases and the plasma levels during the controlled portion of this study.

There was no statistical difference in the number of subjects that had at least one dose increase or one dose decrease of their concomitant AEDs. There was no difference in the number of dose increases or decreases in the two groups. Review of the individual AEDs, revealed that there was no statistical difference in the number of increases or decreases for any of the concmitant AEDs (Figure 25 - Figure 31).

A review of the plasma levels for the concomitant AEDs revealed no significant changes in the plasma levels (Figure 32 - Figure 43).

8.2.2.12 Dosage of Study Medication:

The dose of zonisamide could be adjusted based on adverse events and seizure control (max. trough plasma level of 40 ug/ml or a max. dose of 20 mg/kg). Doses of zonisamide during this study ranged from 100 - 1000 mg, with a mean of 376.9 mg (see Figure 44). In the controlled portion of the study, the zonisamide doses ranged from 100 - 1000 mg, with a mean of 325 mg and a median of 300 mg (see Figure 45).

8.2.2.13 Plasma Levels of Zonisamide

The plasma levels for zonisamide during the trial, including the open-label extension, ranged from 0 - 56.0 (Figure 46), with the maximum level occurring at a dose of 800 mg / day. During the controlled portion of the trial, the zonisamide levels ranged from 0 - 35.0 (Figure 47), with the maximum level occurring with a dose of 1000 mg / day.

8.2.2.14 Study 912-EUR Conclusions:

This study was nearly identical in design to the 912-US study with the exception of dosing, once a day in this study and BID in 912-US. The plasma levels of zonisamide in the controlled portion of the study was slightly less in this study than in the 912-US study. Although this study did not reach statistical significance with respect to the primary outcome measure (except for the evaluable-subjects analysis), the trend was similar to that seen for study 912-US. Likewise, this study did not reach statistical significance (intent-to-treat analysis) with respect to the secondary outcome measure, percent responders. Again, the trend was similar to that seen in the 912-US study.

8.2.3 Study [redacted]922

8.2.3.1 Title:

Placebo-Controlled Efficacy And Safety Evaluation Of Zonisamide In The Treatment Of Seizures In Medically Refractory Patients

8.2.3.2 Objective:

The objectives of this study was to evaluate the efficacy of zonisamide [total daily doses of 100 mg, 200 mg (100 mg BID) and 400 mg (2x100 mg BID) when added to treatment regimens including other antiepileptic drugs (AEDs), compare the incidence of side effects during treatment with zonisamide versus placebo, and to determine steady-state serum levels of zonisamide.

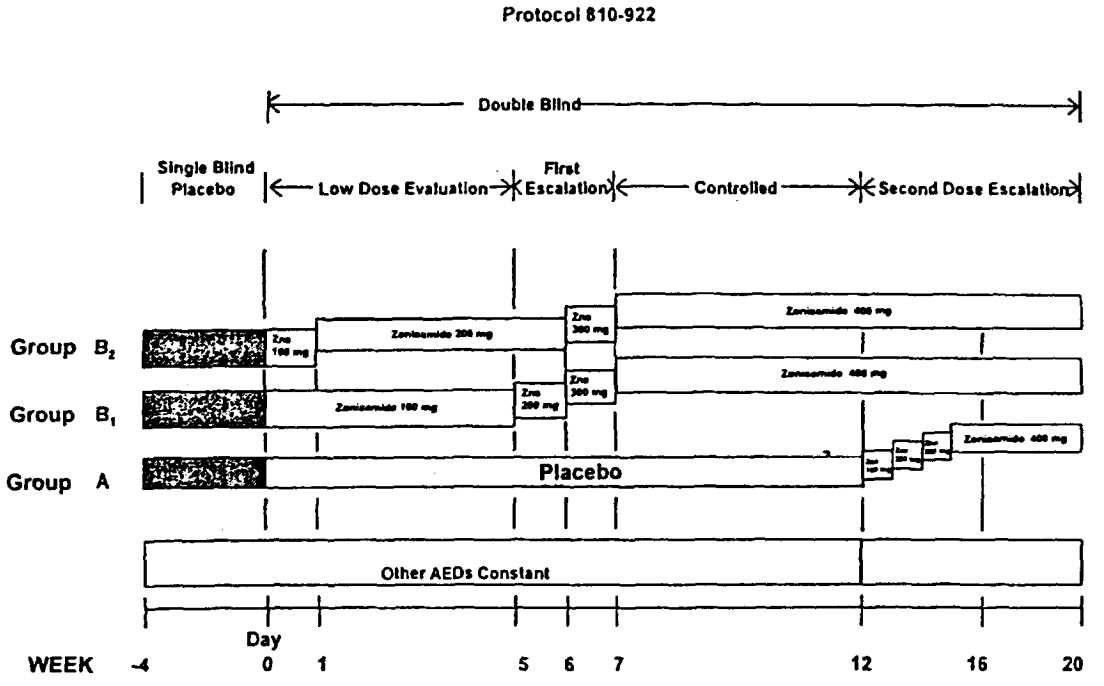
8.2.3.3 Study Dates:

March 24, 1994 to March 5, 1996

8.2.3.4 Study Design:

This study employed a multi-center, placebo-controlled, double-blind, randomized, imbalanced parallel group, fixed incremental doses design (Figure 2).

Figure 2



8.2.3.4.1 Inclusion Criteria

- Patients will be male or female epileptic outpatients at least 12 years of age, of any race.
- Females of childbearing potential must not be pregnant or nursing and must agree to practice, during the study, a reliable form of contraception. Reliable forms of contraception include oral contraceptives, intrauterine devices in place for at least 3 months, surgical sterilization or adequate barrier methods. Females who are postmenopausal for 2 years are eligible or entry. Females who have not reached menarche or are not sexually active may enter at the discretion of the investigator.
- For three months prior to entering the single blind placebo baseline period and throughout this period, each patient must have at least four recognizable partial seizures per month and must not be seizure-free for more than 30 consecutive days.
- **Partial seizures will be complex partial, or recognizable partial onset seizures with a motor component.** Either may be with or without secondary generalization. The International Classification of Epileptic Seizures and Syndromes will be used to classify each patient's seizures.
- Support for the diagnosis of the seizure type should include observation of a seizure by a professional observer (physician, nurse, or technician), or by a reliable witness.
- Current antiepileptic therapy should include at least one but no more than two AEDs. At least one must be a primary AED (phenytoin, carbamazepine, valproic acid, phenobarbital or

primidone). Other AEDs (except investigational AEDs) are acceptable providing one of the primary drugs is present.
- Benzodiazepine use is described in Section VI. G. Concurrent Medications.
- Current treatment must be considered by the investigator to be less than optimal either for lack of control of seizures or unacceptable side effects.
- Patients must be able to keep a reliable calendar of their seizures and accurately record the occurrences in the patient seizure diary.

8.2.3.4.2 Exclusion Criteria

- A history or evidence of a progressive CNS disease or lesion, encephalopathy, or clinically significant organic disease (including unstable cardiac disease, hematological, hepatic, psychiatric or renal disease).
- Any condition which may interfere with the absorption of zonisamide.
- A history of an allergic response to sulfonamide drugs, hemolytic anemia, acute intermittent porphyria, or G-6-PD deficiency.
- A history of chronic excessive alcohol consumption or drug abuse during the last two years.
- Absence seizures.
- Clinical laboratory abnormalities outside of an acceptable range Alkaline phosphatase, LDH, SGOT, and SGPT up to three times the normal upper limit are acceptable if attributed to current AED therapy.
- Any patient not reasonably expected to complete the trial.
- Any investigational drug within 1 month prior to the screen visit.
- Previous treatment with zonisamide.
- .Acetazolamide as an anticonvulsant within one year of study initiation.

8.2.3.4.3 Protocol Amendments:

A single protocol amendment was made to this study on January 30, 1995. The changes included excluding subjects that had received felbamate for 5 months prior to the study and to exclude the use of felbamate during the study. Other changes included the addition of red cell indices and reticulocyte counts to the laboratory evaluations. A third change was that zonisamide would be tapered to discontinuation for subjects who terminated participation after the week 20 visit.

8.2.3.5 Conduct of Study:

8.2.3.5.1 Seizure Data

The International Classification of Epileptic Seizures was used to classify the patient's seizures. The seizures were classified into the following categories in the seizure database: simple partial (SP), simple partial with generalization (SP-G), complex partial (CP), complex partial with generalization (CP-G), Other, and Flurry.

8.2.3.5.2 Investigators / Location:

A total of 203 subjects were randomized at 20 sites in the U.S. The subject enrollment by investigator and site is shown in

Table 18.

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Table 18

Patients Randomized to Each Treatment Group by Investigator/Center				
Investigator Number and Location	**A**	**B1**	**B2**	**Total**
Arlt, G. J., MD (6246; Pittsburgh, PA)	2	2	1	5
Ayala, R., MD (5764; Tallahassee, FL)	11	8	9	28
Barkley, G., MD (5584; Detroit, MI)	2	2	1	5
Bergen, D., MD (5650; Chicago, IL)	4	3	4	11
Beydoun, A., MD (6128; Ann Arbor, MI)	4	3	3	10
Blum, D., MD (6148; Phoenix, AZ)	5	3	3	11
Drake, M. E., MD (6349; Columbus, OH)	4	3	2	9
Ehle, A., MD (7098; Chicago, IL)	2	1	1	4
Faught, E., MD (6123; Birmingham, AL)	7	6	6	19
Ferrendelli, J. A., MD (5586; St. Louis, MO); *replaced by Miller, J., MD (5755; St. Louis, MO)*	2	1	0	3
French, J., MD (5581 Philadelphia, PA)	4	3	3	10
Leppik, I. E., MD (5499; Minneapolis, MN)	6	4	3	13
Montouris, G., MD (6125; Memphis, TN)	8	6	6	20
Morrell, M., MD (5652; Stanford, CA)	3	3	3	9
Morris, G. L., MD (6127; Milwaukee, WI)	6	3	4	13
Ojemann, L., MD (5575; Seattle WA; *replaced by Wilensky, A. J., MD (5502; Seattle, WA)*	2	2	2	6
Ramsay, R. E., MD (5574; Miami, FL)	2	0	1	3
Spitz, M. C., MD (6121; Denver, CO)	4	3	2	9
Willmore, L. J., MD (5585; Houston, TX)	2	0	1	3
Yerby, M. S., MD, MPH (6122; Portland, OR) *replaced by So, N., MD (7332; Portland, OR)*	5	4	3	12
Totals	**85**	**60**	**58**	**203**
Reproduced from the sponsor's submission.				

8.2.3.5.3 Patient Disposition:

Eighty-five percent of the placebo and seventy-two percent of the zonisamide subjects completed the study. Of those discontinuing the study, the majority discontinued due to adverse events, 8.2% and 11.9% for the placebo and zonisamide, respectively. In the zonisamide group, 4.2% discontinued due to lack of efficacy compared to 1.2% in the placebo group. The subject disposition is summarized in Table 19.

Table 19

Summary of Patient Disposition for Study 922-US						
	Group A				Groups B1 + B2	
	PLB (Weeks 1-12) N=85		ZNS (Weeks 13-20) N=72		ZNS (Weeks 1-20) N=118	
Reason	**N**	**%**	**N**	**%**	**N**	**%**
Completed	72	84.7	61	84.7	85	72.0
Discontinued	13	15.3	11	15.2	33	28.0

Adverse Event	7	8.2	5	6.9	14	11.9
Lack of Efficacy	1	1.2	4	5.6	5	4.2
Lack of Compliance	0	0.0	1	1.4	5	4.2
Lost to Follow- Up	0	0.0	1	1.4	2	1.7
Personal Reasons	1	1.2	0	0.0	2	1.7
Other	4	4.7	0	0.0	5	4.2

8.2.3.5.4 Demographics:

The difference in sex distribution in the groups was statistically significant, with a higher percentage of females in the placebo group. The remaining baseline characteristics, including the baseline seizure frequency were comparable in the two groups (see Table 20).

Table 20

Patient Demographic and Baseline Characteristics (Protocol 922-US)

Demographic Characteristic	Group A Placebo/ ZNS N= 85	Zonisamide Group B1 N= 60	Zonisamide Group B2 N= 58
Sex N (%)*			
Male	35 (41%)	37 (62%)	32 (55%)
Female	50 (59%)	23 (38%)	26 (45%)
Race N (%)			
Caucasian	72 (85%)	50 (83%)	51 (88%)
Black	9 (11%)	7 (12%)	4 (7%)
Asian	1 (1%)	1 (2%)	0 (0%)
Other	3 (4%)	2 (3%)	3 (5%)
Age (yr)			
Mean ±SD	34.2 ± 11.4	35.8 ± 11.4	33.6 ± 11.2
Range	(14- 67)	(13- 66)	(15- 68)
Distribution			
12- 40	62 (72.9%)	39 (65.0%)	43 (74.1%)
>40- 65	21 (24.7%)	20 (33.3%)	14 (24.1%)
>65	2 (2.4%)	1 (1.7%)	1 (1.7%)
Mean Age Seizure Onset (yr)			
Mean ±SD	12.2 ± 12.2	12.0 ± 10.7	12.9 ± 11.7
Range	[redacted]		
Weight (kg)			
Mean ±SD	75.0 ± 18.4	81.7 ± 20.3	75.6 ± 18.7
Range	[redacted]		
Baseline Seizure Frequency			
All Partial			
Mean	40.9	23.4	48.0
Median	13.0	11.2	13.0
Range	[redacted]		
Complex Partial			
Mean	29.8	11.5	29.2
Median	7.0	6.2	8.0
Range	[redacted]		
All Seizure Types			
Mean	40.9	23.4	48.3

Median	13.0	11.2	14.0
Range	[redacted]		
Primary Seizure Classification (N/%)			
Complex Partial	65 (77%)	46 (77%)	46 (79%)
All partial	81 (95%)	57 (95%)	57 (98%)
Other	4 (5%)	3 (5%)	1 (2%)

* The difference in sex distribution was significant between Group A and Groups B1+B2; p=0.0152
Reference: Table 3, Clinical Study Report No. DAINU922 (S8-V59-P64).
Reproduced from the sponsor's submission.

8.2.3.5.5 Concomitant Antiepileptic Drugs:

Patients were required to receive at least one but no more than two of the following primary AEDs during the study: phenytoin, carbamazepine, valproic acid, phenobarbital, or primidone. The other concomitant AEDs are listed in Table 21.

Table 21

Other Concomitant Anti-epileptic Medications

	Treatment Group		
	A (N=85)	B1 (N=60)	B2 (N=58)
Medication	**N (%)**	**N (%)**	**N (%)**
Carbamazepine	16 (18.8)	9 (15.0)	11 (19.0)
Carbamazepine + Gabapentin	6 (7.1)	6 (10.0)	7 (12.3)
Phenytoin	8 (9.4)	4 (6.7)	6 (10.3)
Phenytoin + Valproate	9 (10.6)	3 (5.0)	1 (1.7)
Gabapentin + Phenytoin	4 (4.7)	6 (10.0)	2 (3.4)
Carbamazepine + Phenytoin	2 (2.4)	6 (10.0)	3 (5.3)
Carbamazepine + Valproate	4 (4.7)	3 (5.0)	4 (6.9)
Carbamazepine + Primidone	1 (1.2)	4 (6.7)	1 (1.7)
Valproate	3 (3.5)	2 (3.3)	1 (1.7)
Gabapentin + Valproate	3 (3.5)	3 (5.0)	0 (0.0)
Lamotrigine + Phenytoin	1 (1.2)	2 (3.3)	3 (5.2)
Carbamazepine + Phenobarbital	3 (3.5)	2 (3.3)	1 (1.7)
Phenobarbital	2 (2.4)	0 (0.0)	2 (3.4)
Carbamazepine + Lamotrigine	2 (2.4)	1 (1.7)	1 (1.7)
Phenytoin +Phenobarbital	1 (1.2)	1 (1.7)	1 (1.7)
Lamotrigine + Gabapentin	2 (2.4)	0 (0.0)	0 (0.0)
Gabapentin + Phenobarbital	2 (2.4)	0 (0.0)	0 (0.0)
Gabapentin	1 (1.2)	1 (1.7)	0 (0.0)
Carbamazepine + Clonazepam	0 (0.0)	0 (0.0)	2 (3.4)
Carbamazepine + Felbamate	2 (2.4)	0 (0.0)	0 (0.0)
Phenytoin + Primidone	2 (2.4)	0 (0.0)	0 (0.0)
Other AEDs and AED Combinations	11 (12.9)	7 (11.7)	12 (20.7)

Reproduced from the sponsor's submission.

8.2.3.5.6 Concomitant Non-Antiepileptic Drugs:

A review of the concomitant non-AEDs, revealed three subjects that received medications with possible anti-epileptic actions during weeks 0 - 12. Two subjects were in the placebo group (xanax / tranxene) and one in the zonisamide group (versed).

8.2.3.6 Primary Efficacy Measure:

The protocol defined primary efficacy variable was the median percentage change from baseline in seizure frequency. The efficacy of zonisamide 100 mg per day (Group B1) was evaluated by comparing Week 1 to 5 results to placebo (Group A) results. The efficacy of zonisamide 200 mg per day (Group B2) was evaluated by comparing Week 2 to 6 results to placebo (Group A) results. The efficacy of zonisamide 400 mg per day (Group B) was evaluated by comparing Week 8 to 12 results to placebo (Group A) results during Week 8 to 12.

8.2.3.7 Analysis Plan:

The analysis plan for this study was similar to that described for the two previous studies. The labeling convention for the four populations was different for this study. The primary efficacy analysis was all intent-to-treat (ITT) patients receiving at least one dose of study drug (zonisamide 400 mg/day or placebo) during Weeks 8 through 12 of the double-blind phase without the use of imputed seizure rate values for patients who withdrew prior to Week 8 (Population 1). This would correspond to population 3 in the studies 912-US and 912-EUR.

8.2.3.8 Primary Efficacy Analysis:

The intent-to-treat without imputation analysis is statistically significant with a greater reduction in seizure frequency for all partial seizures in weeks 8 - 12 in the zonisamide group (Table 22). The reduction in seizure frequency was statistically significant for all partial seizures and all seizures, but not for complex partial seizures (Table 23). The Median Percentage Change From Baseline in Seizure Frequency was statistically significant for all partial seizures when placebo was compared to Zonisamide, Group B1 (100 mg/day) and Group B2 (200 mg/day), with p-values of 0.0376 and 0.0031, respectively.

Table 22

Reduction From Baseline in the Frequency of All Partial Seizures for Study 922-US Weeks 8-12

	Zonisamide (Group B1 + B2)		Placebo (Group A)		
Population	N	Median % Change	N	Median % Change	p- value
1 a	98	-40.5	72	-9.0	0.0091
2 b	117	-29.0	85	-2.6	0.0094
3 c	94	-40.5	70	-9.7	0.0273

a Intent-to-treat analysis using data from Weeks 8 through 12 of the double-blind phase, with no imputation of data for patients withdrawing prior to Week 8
b Same as intent-to-treat population but with imputation of "worst-case" values for patients withdrawing before Week 8;

c Efficacy-evaluable population: ITT patients having at least four partial seizures during the single-blind phase, and at least (through Week 9) two weeks exposure tozonisamide 400 mg/day; Group A withdrawals had to have continued in study through Week 9 or longer; patients withdrawn for a protocol violation were excluded.
Reference: Appendices C.9.1, C.9.2, D.15.1 through D.15.4

Table 23

Median Percentage Change From Baseline in Seizure Frequency Weeks 8-12 Intent-to-treat Analysis by Seizure Type

		Placebo (Group A)		Zonisamide (Group B1 + B2)		
Analysis Population	**Seizure Type**	**N**	**% Change**	**N**	**% Change**	**p-Value**
Population 1 (Primary) a	All Partial	72	-9.0	98	-40.5	0.0091
	Complex Partial	66	-11.7	87	-37.8	0.0883
	All Seizures	72	-9.0	98	-40.5	0.0109

a Intent-to-treat analysis using data from Weeks 8 through 12 of the double-blind phase, with no imputation of data for patients withdrawing prior to Week 8

8.2.3.9 Secondary Efficacy Measures:

The secondary efficacy variable is the response rate for the combined zonisamide 400 mg/day groups (B1+B2) versus placebo (Group A) during Weeks 8 to 12. The response rate is defined as the percentage of patients, termed "responders", achieving 50% or greater reduction in seizure frequency relative to the baseline seizure rate.

8.2.3.10 Secondary Efficacy Analysis:

The percentage of responders (≥ 50% reduction from baseline in seizure (all partial) frequency - weeks 8-12) was statistically significant with a larger percentage of responders in the zonisamide group compared to the placebo group (see Table 24). The percentage of responders for all partial seizures was statistically significant when either B1 or B2 was compared to placebo.

Table 24

Percentage of Patients with ≥ 50% Reduction From Baseline in Seizure Frequency - Weeks 8-12

	Treatment				
	Placebo		Zonisamide Group B1 + B2 (400 mg / day)		
Seizure Type	n / N	%	n / N	%	p- Value
All Partials	16 / 72	22.2	41 / 98	41.8	0.0137
Complex Partial	18 / 66	27.3	35 / 87	40.2	0.1818
All Seizures	16 / 72	22.2	41 / 98	41.8	0.0137

8.2.3.11 The Role of Concomitant AEDs:

The role of concomitant AEDs in the efficacy of zonisamide was evaluated by examining the dose increases and decreases and the plasma levels during the controlled portion of this study. It should be noted that the number of visits during the controlled portion of this study were fewer than those seen in the 912-US and 912-EUR studies. Some subjects had no visits recorded, in the database, for the controlled portion of the trial. This lack of visits potentially limits the usefulness of this evaluation.

There was no statistical difference in the number of subjects that had at least one dose increase or one dose decrease of their concomitant AEDs. There was no difference in the number of dose increases or decreases in the two groups. Review of the individual AEDs, revealed that there was no statistical difference in the number of increases or decreases for any of the concomitant AEDs, except the other category, with the placebo group having a statistically significant greater number of dose reductions (Figure 48 - Figure 53).

A review of the plasma levels for the concomitant AEDs revealed no significant changes in the plasma levels (Figure 54 - Figure 65).

8.2.3.12 Dosage of Study Medication:

In contrast to the two previously reviewed studies, this study employed a fixed dose. During the controlled portion of the trial the dose was 400 mg.

8.2.3.13 Plasma Levels of Zonisamide

The plasma levels for zonisamide during trial, including the open-label extension, ranged from 0 - 74.33 (please see Figure 66 and Figure 67), with the maximum level occurring at a dose of 400 mg / day. The same values were obtained for the controlled portion of the study.

8.2.3.14 Study 922-US Conclusions:

Study 922-US was positive on both the primary and secondary outcome measures in the intent-to-treat population. Similar results were obtained for the lower dose comparisons (100 mg and 200 mg). The use of other concomitant antiepilepsy drugs (AEDs) did not appear to affect the outcome of this study. The use of concomitant AEDs was approximately equal in the two groups, placebo and zonisamide. There number of concomitant AED dose adjustments were comparable in the two groups. Finally, the number of subjects in the two groups who received "non-AED" medications with possible AED effects was comparable. The results of this study support zonisamide as an effective add-on treatment in patients with partial seizures.

9. Safety Review:

A separate safety review will be prepared by the Clinical Safety Review Team.

10. Conclusions Regarding Efficacy Data:

The sponsor has provided sufficient clinical and statistical evidence to establish that zonisamide is efficacious as adjunctive therapy for the treatment of patients with partial seizures.

11. Labeling Review:

Three sections of the proposed labeling will be reviewed with respect to the reviewed efficacy data; clinical studies, indications and usage, and dosage and administration.

11.1 Clinical Studies:

In the clinical studies section, the sponsor has presented the results of two (912-US and 922-US) controlled studies. The results of 912-EUR have not been included.

11.2 Indications And Usage:

The sponsor has proposed that Zonisamide is indicated as adjunctive therapy in the treatment of partial seizures with and without secondary generalization in adults with epilepsy. The sponsor has not provided efficacy data to support the use of zonisamide for the secondary generalization seen with some partial seizures. The following statement is recommended: Zonisamide is indicated as adjunctive therapy in the treatment of partial seizures in adults with epilepsy. Safety (safety to be addressed by a separate review) and effectiveness in pediatric patients below the age of 16 have not been established.

11.3 Dosage and Administration:

The design of the two studies which support the efficacy of zonisamide employed different dosing. The 922-US study employed a fixed incremental doses design and the 912-US study employed an adjustable dose design with the maiximum dose employed during the controlled portion of the study of 900 mg / day. Both the 100 mg/day and the 200 mg/day groups of the 922-US study demonstrated a statistically significant reduction in seizure frequency as determined by the primary outcome measure, the median percentage change from baseline in seizure frequency. The sponsor has recommended an initial dose of 200 mg po BID. The efficacy results at a 200 mg daily dose are discussed in the clinical studies section. A statement concerning the efficacy of 100 mg and 200 mg daily doses should be included in labeling. The sponsor notes that doses of up to 1,500 mg / day have been given to humans. This statement should be amended to include

that the highest dose used in humans in controlled studies demonstrating efficacy was 900 mg / day.

12. Recommendation:

It is recommended, based on the review of efficacy data, that zonisamide be deemed approvable. This recommendation is contingent upon a similar finding by the safety review team.

/S/

James H. Sherry, M.D., Ph.D.
Medical Reviewer

cc:
HFD-120
HFD-120/Leber/Katz

13. Appendix

Table 25

General Pharmacokinetics (Absorption, Distribution, Metabolisim, And Elimination / Excretion) In Healthy Volunteers

Protocol Number	Treatment Group	Dosage Form*	Dose	Cmax (ug/ml)	Tmax (hr)	Vd/F (L/kg)	AUC(0-∞) ug/ml•hr	t ½ (hr)	Urinary Excretion	CL/F (ml/min/kg)	Comments
912-4 Single Dose	200 mg	100 mg Capsule	3 randomized administrations of single 200-, 400-, or 800-mg doses. 3-week washout between doses.	2.27	2.4	1.77	170	62.5[b]	16.0%	0.315	See Table 6-3 for complete description of treatment regimen.
	400 mg			5.16	2.8	1.47	347	52.1[b]	14.6%	0.316	
	800 mg			12.15	3.6	1.09	863	49.7[b]	16.6%	0.252	
810-924 Multiple Doses	200 mg BID	100 mg Capsule	200 mg BID for Days 15-35.	30.3	2.1		340	68.6		0.130	Sec Table 6-3 for complete description of treatment regimen. AUC values are at steady-state. Cl/F is measured in L/hr.
	400 mg QD		400 mg QD for Days 15-35.	28.0	1.8		302.0	63		0.155	

a Numbers in this table not expressly associated witn individual patient results are means unless stated otherwise;
b Harmonic mean; () = percent relative standard deviation;
BID = twice daily; QD = once daily

*All oral administration

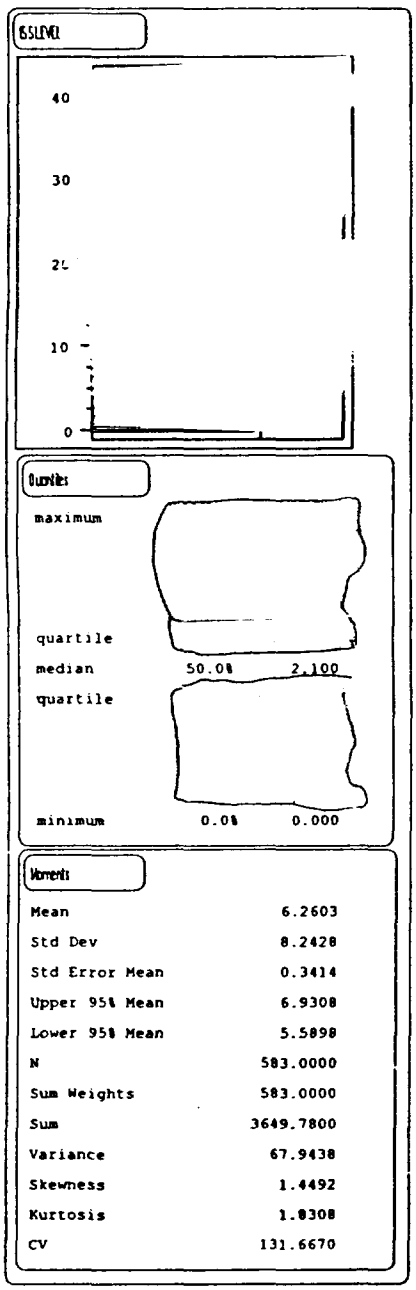
Table 26

Summary Of Efficacy* Studies for Zonisamide								
	Number of Patients		Median Percent Change From Baseline			Percent Responders		
Study	Zonisamide	Placebo	Zonisamide	Placebo	p- value	Zonisamide	Placebo	p- value
912-US	78	74	-25.4	2.2	0.0003	24.4	12.2	0.055
912-EUR	72	71	-24.8	2.9	0.117	25.0	14.1	0.1053
922-US	98	72	-40.5	-9.0	0.0091	41.8	22.2	0.0137

* for all partial seizures
Intent-to-treat defined as using all post-randomization data with no imputation.

Figure 3

Zonisamide Levels During the Controlled Portion of 912-US



APPEARS THIS WAY
ON ORIGINAL

Figure 4

Zonisamide Levels in 912-US

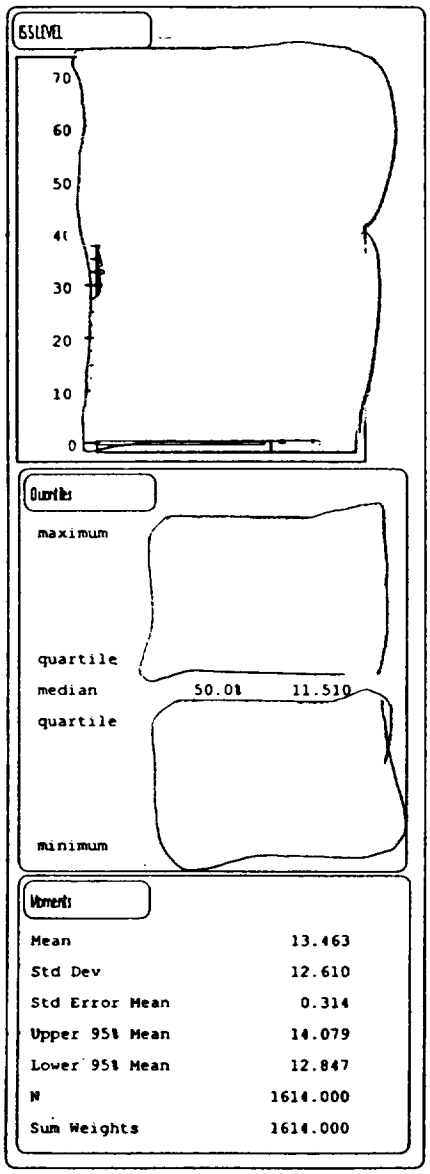


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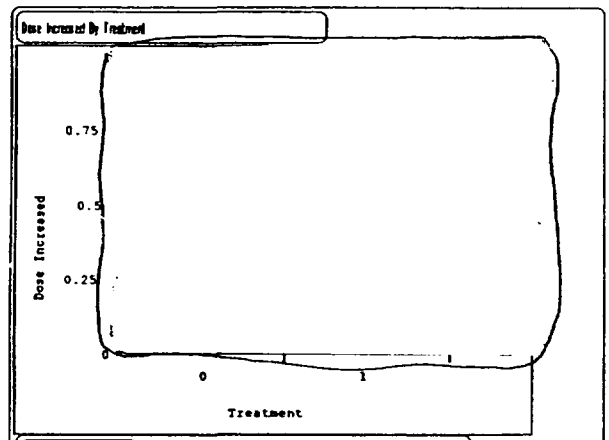
Figure 5

Subjects with Dose Increases of Concomitant AEDs in 912-US by Treatment (0=placebo; 1=zonisamide)



Crosstabs

	Treatment		
Count / Col %	0	1	
Dose Increased 0	64	64	128
	87.67	82.05	
Dose Increased 1	9	14	23
	12.33	17.95	
	73	78	151

Tests

Source	DF	-LogLikelihood	RSquare (U)
Model	1	0.465045	0.0072
Error	149	63.967969	
C Total	150	64.433015	
Total Count	151		

Test	ChiSquare	Prob>ChiSq
Likelihood Ratio	0.930	0.3348
Pearson	0.922	0.3368

Fisher's Exact Test	Prob
Left	0.8827
Right	0.2321
2-Tail	0.3724

Kappa	Std Err
0.054874	0.056786

Kappa measures the degree of agreement.

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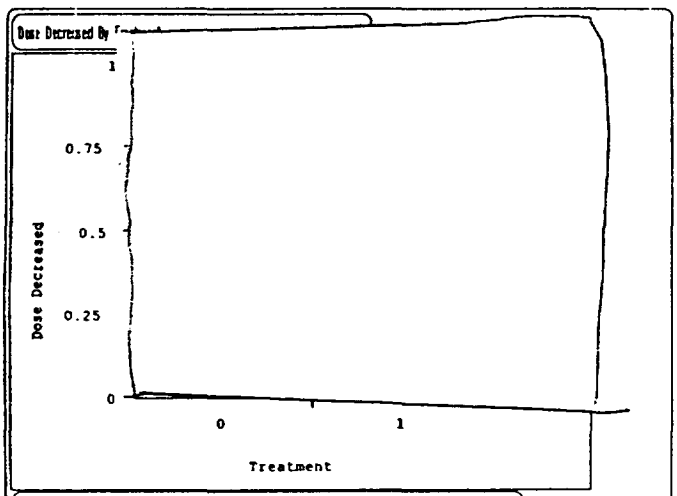
ON ORIGINAL

Figure 6

Subjects with Dose Decreases of Concomitant AEDs in 912-US by Treatment (0=placebo; 1=zonisamide)



Crosstabs

Dose Decreased	Count / Col %	Treatment 0	Treatment 1	
	0	63	51	114
		86.30	65.38	
	1	10	27	37
		13.70	34.62	
		73	78	151

Tests

Source	DF	-LogLikelihood	RSquare (U)
Model	1	4.605883	0.0548
Error	149	79.472786	
C Total	150	84.078669	
Total Count	151		

Test	ChiSquare	Prob>ChiSq
Likelihood Ratio	9.212	0.0024
Pearson	8.918	0.0028

Fisher's Exact Test	Prob
Left	0.9994
Right	0.0023
2-Tail	0.0042

Kappa	Std Err
0.205469	0.066855

Kappa measures the degree of agreement.

Figure 7

Number of Dose Increases (Upper) or Decreases (Lower) of Concomitant AEDs in 912-US by Treatment (0=placebo; 1=zonisamide)

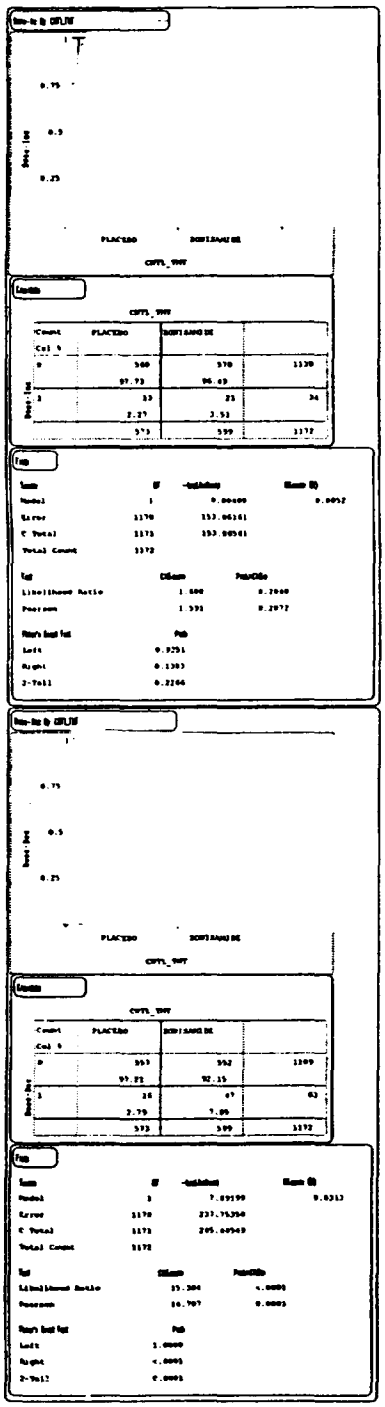


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Figure 8

Number of Dose Increases (Upper) or Decreases (Lower) of Carbamazepine in 912-US by Treatment (0=placebo; 1=zonisamide)